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The Oxidation of Amines with Sulfonyl Peroxides. 3. Regioselectivities and Substituent Effects in the Oxidation of Benzylamines, and Kinetic Evidence for a Two-Electron Pathway[1]

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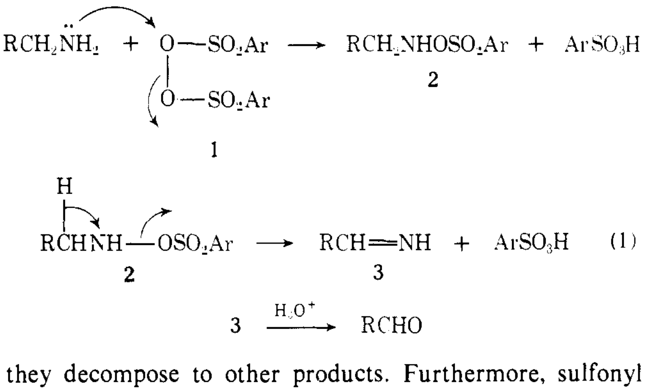
Abstract: A series of substituted primary benzylamines was oxidized with *p*-nitrobenzenesulfonyl peroxide (**1a**), and the results from substituent effects and kinetic studies favor a two-step, two-electron mechanism for this oxidation. The first step is nucleophilic attack by the amine on the peroxide bond which yields a hydroxylamine-*O*-*p*-nitrobenzenesulfonate adduct, **2**. Substituent effects for this step (k_1) were determined by the competitive method and from a Hammett plot, $\rho = -0.53$. Conductometric methods were used to study the rate constants for the second step (k_2), which is base-catalyzed elimination of **2** to the imine. For this, the slower step, Hammett treatment of the rate data gives $\rho = 0.24$ and $k_H/k_D = 4.2$. The regioselectivities for the oxidative deamination of *N*-alkylbenzylamines, **8**, were determined and are also consistent with the preferred two-electron oxidative pathway. The kinetics and substituent effects of imine-forming eliminations are available from this study, and the results are compared to analogous olefin-forming eliminations.

Amine oxidations display a rich diversity of mechanisms which depend on the oxidant, the amine type, the pH, and/or metal additives.[3] The reaction of amines with oxidants can occur at the nitrogen lone pair by one-electron or two-electron oxidation or reaction can occur at the α carbon atom by hydrogen abstraction. In fact a given oxidant may follow different pathways with different amines or competing pathways with the same amine.

It has been reported that arylsulfonyl peroxides $(ArSO_2O)_2$, **1**, react with a variety of primary and secondary amines to give oxidative deamination.[1b,4] This reaction is characterized by a general insensitivity of the reaction to amine structure, and aryl rearrangement to nitrogen where α hydrogens are lacking or where good migrating groups are present.[1a] Based on these observations, the process can be described mechanistically as a two-step, two-electron oxidation (eq 1). The first step is nucleophilic attack by the amine on the peroxide bond to give a hydroxylamine-*O*-arylsulfonate adduct **2**. The second step, which may be base catalyzed, is elimination of arylsulfonic acid from **2** to give the product imine **3** which can be isolated. Hydrolysis to the carbonyl compound completes oxidative deamination of the amine.



Amines are well known to react nucleophilically with peroxides, particularly acyl peroxides, yielding *O*-acylhydroxylamines.[5] These can be isolated[5e] in certain cases, but in solution they decompose to other products. Furthermore, sulfonyl peroxides react electrophilically with π donors by two-electron donation to the peroxide bond.[6] The second step of eq 1 is elimination of arylsulfonic acid to give the imine product. Eliminations to give carbon–nitrogen π bonds have been discussed for nitrile-forming eliminations from imines[7] and for imine formation from *N*-halo amines.[8] The good leaving ability of the arylsulfonate group in **2** would promote such a polar elimination.

While there exist good and precedented arguments for the mechanism depicted in eq 1, several alternate pathways can account for the observed products. These involve free-radical

Table I. Competitive Oxidation of Benzylamines ($XC_6H_4CH_2NH_2$, $C_6H_5CH_2NH_2$) with *p*-NBSP

Entry	Amine pair	Substituents (X)	$k_{1\,rel}$	Log $k_{1\,rel}$
1	**4b, 4a**	*p*-CH_3	1.41	0.149
2	**4c, 4a**	*m*-CH_3	1.20	0.079
3	**4d, 4a**	*p*-Cl	0.82	−0.086
4	**4e, 4a**	*m*-Cl	0.75[a]	−0.124
5	**4f, 4a**	*m*-CF_3	0.64	−0.193
6	**4d, 4c**	*p*-Cl, *m*-CH_3	0.69[b]	

[a] Total yield of carbonyl products was 75%. [b] $k_{1\,rel} = 0.68$ calculated from entries 3 and 2.

intermediates and are thus one-electron pathways. Electron transfer from the amine to the peroxide would yield an aminium cation radical which could give **3** by hydrogen abstraction or proton loss followed by oxidation of the resulting radical (eq 2).

$$\begin{array}{l} RCH_2NH_2 + (ArSO_2O)_2 \rightarrow \\ \quad RCH_2N^+\dot{H}_2 + ArSO_3\cdot + ArSO_3^- \rightarrow \mathbf{3} + 2ArSO_3H \\ \quad\quad\quad \downarrow{\scriptstyle -H^+} \\ [R\dot{C}H\text{–}\ddot{N}H_2] \rightarrow \mathbf{3} \end{array} \qquad (2)$$

Electron transfer is known for amine oxidations with chlorine dioxide,[9] alkaline potassium hexacyanoferrate(III),[10] and is perhaps a contributing pathway in some amine oxidations using acyl peroxides.[11] The controversy over the involvement of electron transfer in amine–peroxide reactions is still unsettled.

Another one-electron possibility is that nucleophilic attack by the amine on the peroxide to give **2** is followed by homolytic N–O bond fission to give radicals which proceed to products (eq 3). Such a pathway has been favored for the reaction of tertiary amines with acyl peroxides.[5a,12]

$$RCH_2NH_2 \quad + \quad (ArSO_2O)_2$$

$$\longrightarrow \mathbf{2} \begin{array}{l} \xrightarrow{H^+} RCH_2\overset{\cdot\,+}{N}H_2 \;+\; ArSO_3\cdot \longrightarrow \\ \searrow \; RCH_2\underset{\cdot\cdot}{\dot{N}}H \;+\; ArSO_3\cdot \; \nearrow \end{array} \mathbf{3} \qquad (3)$$

In order to use the oxidation of amines by sulfonyl peroxides to synthetic advantage and to develop it as a possible method for studying two-electron oxidations of nitrogen, a greater insight into mechanistic detail was required. Herein are described results of experiments using substituted benzylamines, **4**, and *N*-alkylbenzylamines, **8**, with *p*-nitrobenzenesulfonyl peroxide (p-NBSP, **1a**), which indicate that the mechanism in eq 1 obtains in this oxidation.

Results

The two-step, two-electron mechanism can be formalized as two consecutive reactions with their corresponding rate constants k_1 and k_2 (eq 4, 5). The elimination step may be base catalyzed so that k_2 may be a first- or second-order rate constant (eq 5 and 5a).

$$\mathbf{4} + \mathbf{1a} \xrightarrow{k_1} \mathbf{2} \qquad (4)$$

$$\mathbf{2} \xrightarrow{k_2} \mathbf{3} \qquad (5)$$

and/or

$$\mathbf{2} + \mathbf{4} \xrightarrow{k_2} \mathbf{3} \qquad (5a)$$

The effects of substituents for substituted benzylamines, **4**, on k_1 and k_2 can be predicted based on this mechanism. For eq 4, electron-withdrawing substituents should decrease and electron-donating ones should enhance the nucleophilicity of **4** toward **1a** and thus a negative ρ should be found for the substituent dependence of k_1 in a Hammett treatment. Conversely, in the elimination step, electron-withdrawing substituents would acidify the benzylic proton and speed the rate of elimination while electron-donating substituents would behave oppositely, and a positive ρ value would be observed.

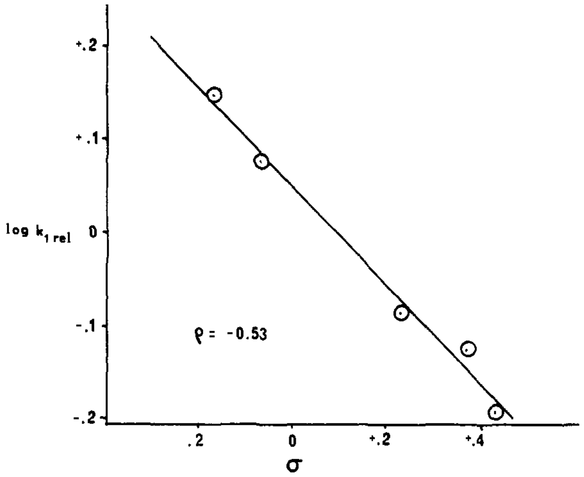


Figure 1. Hammett plot of $k_{1\,rel}$ (competitive) for the reaction of **4a–f** with **1a**.

Mixtures of benzylamine (**4a**) and a substituted analogue, **4b–f**, were treated in the competitive method with **1a** and, after hydrolysis, yielded mixtures of benzaldehydes, **5** (eq 6).

$$\underset{\mathbf{4b\text{–}f}}{XC_6H_4CH_2NH_2} + \underset{\mathbf{4a}}{C_6H_5CH_2NH_2} \xrightarrow[2.\ H^+,\ H_2O]{1.\ \mathbf{1a},\ EtOAc} \underset{\mathbf{5b\text{–}f}}{XC_6H_4CHO} + \underset{\mathbf{5a}}{C_6H_5CHO} \qquad (6)$$

a, X = H
b, X = *p*-CH_3
c, X = *m*-CH_3
d, X = *p*-Cl
e, X = *m*-Cl
f, X = *m*-CF_3

Since the attack of the amine on the peroxide is irreversible,[13] the first-formed amine adduct **2** will lead to the eventual carbonyl product **5** after hydrolysis. By measuring the ratio of carbonyl products, the relative nucleophilicities of substituted benzylamines toward **1a** were determined and thus the value of $k_{1\,rel}$ for eq 4 as a function of substituent. The results are given in Table I. As a check of internal consistency, a mixture of *p*-chlorobenzylamine (**4b**) and *m*-methylbenzylamine (**4d**) was oxidized with **1a** (entry 6).The $k_{1\,rel} = 0.69$ determined for this amine pair is in excellent agreement with the value of 0.68 calculated from the relative reactivities of the individual amines (entries 2 and 3). Furthermore, a 75% yield of carbonyl products was obtained in the oxidation of the **4e–4a** mixture indicating that competing side reactions were unimportant.

The relative rate data for k_1 were plotted vs. the σ values for each substituent[14] and a linear regression analysis of the data gave $\rho = -0.53$ ($r = 0.99$) (Figure 1). A plot vs. σ^+ constants[15] gave a worse correlation.

The oxidation of benzylamines **4** by **1a** yields 2 equiv of *p*-nitrobenzenesulfonic acid (**6**). Since an excess of the amine was present, the acid converted to the benzylammonium *p*-nitrobenzenesulfonate (**7**). The kinetics of the oxidation of **4** with **1a** could therefore be followed by measuring the increase in conductance of a reaction mixture due to the formation of **7**.

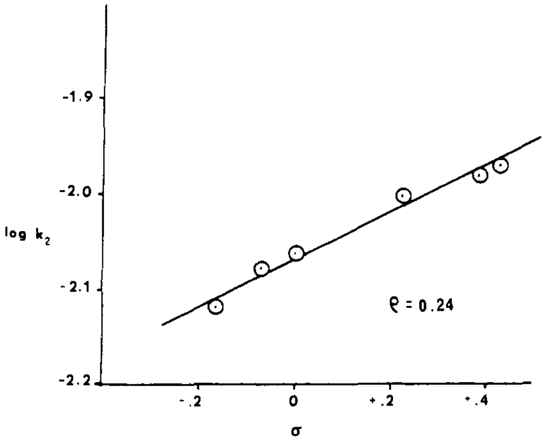


Figure 2. Hammett plot of log k_2 vs. σ for the imine formation step (eq 8).

Table II. Second-Order Rate Constants for Imine Formation (**2** → **3**) in the Oxidation of Substituted Benzylamines at −9.7 ±0.1 °C

Benzylamine	Substituent	k_2, $M^{-1}\ s^{-1}$
4a	H	8.67×10^{-3}
4b	p-CH_3	7.64×10^{-3}
4c	m-CH_3	8.37×10^{-3}
4d	p-Cl	9.97×10^{-3}
4e	m-Cl	1.05×10^{-2}
4f	m-C_3	1.07×10^{-2}
4g	-α,α-d_2	2.05×10^{-3}

Table III. Oxidation of Substituted Benzylamines (**4a-f**) with p-NBSP

Amine	Product	Yield, %[a]
4a	C_6H_5CHO	84
4b	$4\text{-}CH_3C_6H_4CHO$	70
4c	$3\text{-}CH_3C_6H_4CHO$	83
4d	$4\text{-}ClC_6H_4CHO$	82
4e	$3\text{-}ClC_6H_4CHO$	80
4f	$3\text{-}CF_3C_6H_4CHO$	96

[a] Isolated yields measured by gas chromatography.

Table IV. Oxidation of N-Alkylbenzylamines with p-NBSP[a]

Amine	N-Alkyl group	% C_6H_5-CHO[b]	% $C_6H_5CH_2$-NH_2[b]	Benzyl H:alkyl H[c]
2a	CH_3	74	22	5.0:1
2b	CH_2CH_3	58	27	2.1:1
2c	$CH(CH_3)_2$	49	34	0.72:1
2d	$CH_2(CH_2)_5CH_3$	66	31	2.1:1

[a] Carried out with 3 equiv of the amine in ethyl acetate at −78 °C. [b] Isolated yields measured by gas chromatography. [c] Corrected statistically for the numbers of benzylic and alkyl protons. [d] Heptanal was measured instead of benzylamine; however, the yields should correspond.

An advantage to this method was that only very dilute solutions were required and at these concentrations the reaction could be followed easily by periodic conductance readings.

A solution of benzylamine (**4a**) in 3 M water in tetrahydrofuran was mixed in a conductivity cell with a solution of **1a** in ethyl acetate. The final reaction mixture was 0.02-0.05 M in **4a** and 7.5×10^{-4} M in **1a**. Conductance readings revealed that *upon mixing*, at −9.7 °C, a conductance increase occurred which corresponded exactly to the formation of 1 equiv of benzylammonium p-nitrobenzenesulfonate (**7a**). Continued observation of the mixture showed that a second equivalent of **7a** was formed in a slower reaction.

The above stoichiometry was determined from standard solutions of salt **7a** whose conductance was found to be linear with concentration. Thus conductance measurements are a valid method to follow the reaction kinetically and ion pairing phenomena are minimized in the solvent mixture employed (or at least remain constant over the concentration range employed).

Relative to the two-step mechanism in eq 1, it appears that nucleophilic attack by the amine on the peroxide is fast compared with the elimination step of the reaction. Furthermore, use of conductance measurements permits kinetic study of substituent effects on the imine-forming elimination (k_2).

A series of substituted benzylamines, **4a-f**, was reacted with **1a** and the rates of reaction were followed by conductance. An excess of the amine was employed so that pseudo-first-order behavior was observed. Reactions were followed through at least 2 half-lives (usually more than 3) and infinity values were determined. Plots of the conductance data vs. time (see Experimental Section) gave good linear fits by least-squares analysis ($r > 0.99$) and yielded pseudo-first-order rate constants (k_{obsd}). Several amine concentrations were used and the data fit the relationship $k_{obsd} = k_2[A]$ within experimental error. Values of the second-order rate constants, k_2, were derived from plots of k_{obsd} vs. [A] (Table II). Therefore eq 5a describes the elimination step accurately. A Hammett plot of log k_2 vs. σ gave a straight line and $\rho = 0.24$ ($r = 0.99$) (Figure 2).

To ensure that the measured kinetics corresponded to the oxidative deamination reaction, yields of carbonyl products **5a-e** were measured (Table III). The high yields of carbonyl products minimize the contributions of secondary pathways so that mechanistic discussion can be focused on oxidative deamination.

The kinetic isotope effect (KIE) on the elimination step was measured for the oxidation of benzylamine and benzylamine-α,α-d_2 (**4g**). From their respective second-order rate constants of 8.67×10^{-3} and $2.05 \times 10^{-3}\ M^{-1}\ s^{-1}$, a $k_H/k_D = 4.2$ was found for the elimination.

As a further mechanistic test, the oxidation of N-alkylbenzylamines (**8a-d**) was carried out and the regioselectivity of elimination was measured (eq 7). Two modes of oxidative

$$\underset{\mathbf{8}}{C_6H_5CH_2NHCHR_1R_2} + \mathbf{1a} \rightarrow \underset{\mathbf{9}}{C_6H_5CH{=}NCHR_1R_2} + \underset{\mathbf{10}}{C_6H_5CH_2N{=}CR_1R_2} \qquad (7)$$

a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$
d, $R_1 = H$; $R_2 = n\text{-}C_6H_{13}$

cleavage are possible in these unsymmetric systems giving either N-benzylidenealkylamine, **9**, or N-alkylidenebenzylamine, **10**, by removal of a hydrogen atom/proton from the benzyl or alkyl group, respectively. The regioselectivity was determined by measuring the amount of benzaldehyde and the amount of benzylamine present after hydrolysis. The quantities of these compounds reflect the amounts of **9** and **10** produced in the oxidation and their ratio (corrected statistically) is the regioselectivity of the oxidation (Table IV). The regioselectivities measured represent the kinetic product distribution. Although the isomerization **9** → **10** is possible, it requires strong base catalysis. The nearly neutral conditions employed in the present study render such isomerization unlikely.[16] To ensure that the benzylamine produced came from imine **10** and not from undetected side reactions, N-(n-heptyl)benzylamine (**8d**), was oxidized and both carbonyl products, benzaldehyde and heptanal, were measured. The yield of heptanal (31%), and hence the implied yield of benzylamine, was in satisfactory agreement with the yield of benzylamine (27%) obtained in the structurally analogous **3b**, and the regioselectivities obtained were identical (Table IV). A sevenfold change in reactivity (benzylic hydrogens to α-alkyl hydrogens) was noted as the alkyl group was varied from methyl to isopropyl.

Discussion

The substituent effects determined in the present study are most consistent with the two-step mechanism set forth in eq 1. The ρ value of -0.53 determined for the first step of oxidation indicates developing cationic character on nitrogen during the transition state. While this finding is compatible with a nucleophilic attack by the amine on the peroxide, it does not specifically exclude an electron transfer as the first step.

The magnitude of ρ, however, is lower than that of the pK_a dependence of substituted benzylamines, $\rho = -1.045$.[17] For comparison purposes, methylation of substituted *N,N*-dimethylbenzylamines with methyl iodide in methanol gives $\rho = -0.62$,[18] which is lower than the pK_a dependence of $\rho = -1.14$[9b] for these amines. On the other hand, ClO_2 oxidation of these amines by electron transfer has $\rho = -0.92$,[9b] which is similar to the pK_a dependence. The ρ value for the first step of amine oxidation by sulfonyl peroxides is seen to be similar to that for methylation of *N,N*-dimethylbenzylamines. It is apparent that lower values of $|\rho|$ are expected for nucleophilic reactions than for electron transfer oxidations of amines. While both reactions yield positively charged nitrogen products, the latter gives a valence septet while the former retains the octet structure of nitrogen. Thus a greater electron deficiency is developed for electron transfer oxidation and hence a larger magnitude of $|\rho|$.

The small value of $\rho = -0.53$ for the first step of benzylamine oxidations by sulfonyl peroxides is therefore supportive of nucleophilic interaction of the amine with the peroxide, to the extent that small ρ values can be used to distinguish mechanism. The poorer correlation of the relative rate data for k_1 with σ^+ constants argues against benzylic hydrogen abstraction as being the first step. Such a σ^+ correlation is observed for substituted benzylamine oxidations by $KMnO_4$ where hydrogen abstraction is postulated as the rate-determining step.[19]

The use of conductance methods permitted the kinetic study of the imine-forming elimination. The rapid conductance increase upon mixing corresponds to the nucleophilic attack of the amine on the peroxide to give the *N*-benzylhydroxylamine *O*-*p*-nitrobenzenesulfonate (**11**) and 1 equiv of *p*-nitrobenzenesulfonic acid as the benzylammonium salt, **7** (eq 8). The elimination step to the imine product is slower and produces a second equivalent of **7** and this is the step observed kinetically (eq 9).

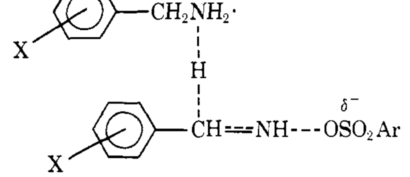
$$\underset{\textbf{4}}{XC_6H_4CH_2NH_2} + \textbf{1a} \xrightarrow[\text{fast}]{k_1} \underset{\textbf{11}}{XC_6H_4CH_2NHOSO_2Ar} + ArSO_3H \xrightarrow{\textbf{4}} \underset{\textbf{7}}{ArSO_3^-XC_6H_4CH_2NH_3^+} \quad (8)$$

$$\textbf{11} + \textbf{4} \xrightarrow[\text{slow}]{k_2} XC_6H_4CH{=}NH + \textbf{7} \quad (9)$$

The rate of elimination is first order with respect to **11** since excellent first-order behavior was found through several half-lives. The rate was also dependent on the amine concentration and thus pseudo-first-order conditions were maintained with an excess of amine. The amine dependence implies that the elimination is base catalyzed.

This kinetic behavior casts doubt on mechanistic alternatives to eq 1. Electron transfer (eq 2), while exhibiting a first-order dependence on amine concentration, yields 2 equiv of **7** from the rate-determining step since subsequent steps to products are fast.[9] Thus a steady increase in **7** in predicted instead of the fast then slow behavior observed. Furthermore, while a two-step scheme is operative in eq 3, the second step is homolysis of the N–O bond of **11** for which amine catalysis seems unlikely. Therefore the most viable alternatives to eq 1 are not supported by the kinetic evidence.

For the amine-catalyzed elimination reaction (eq 9), substituted benzylamines, **4a–f**, yielded a reaction constant $\rho_{\text{obsd}} = 0.24$ from a Hammett plot of the second-order rate constants, k_2. It is to be noted that there is a dual substituent effect operative as shown in **12**. That is, a substituent can influence the rate of elimination by changing the acidity of the benzylic protons, ρ_a, and by changing the basicity of the amine catalyst, ρ_b. These substituent effects are opposite in effect; ρ_a is positive while ρ_b is negative in sign. Hence ρ_{obsd} can be expressed $\rho_{\text{obsd}} = \rho_a + \rho_b$.



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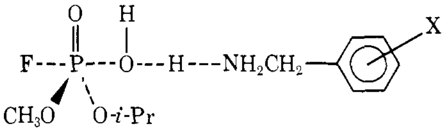
In order to evaluate ρ_a and compare it to other eliminations involving benzylic protons, ρ_b must be deduced. The use of substituted benzylamines as base catalysts has apparently not been investigated in any detail. However, for the amine-catalyzed hydrolysis of isopropyl methylphosphonofluoridate, *p*-methoxybenzylamine and benzylamine were used and gave second-order rate constants of 2.46 and 2.04 M^{-1} min^{-1}, respectively.[17b] For these two points, $\rho_b = -0.30$ in a reaction in which a proton is being removed from water in the transition state, **13**. Furthermore, $\rho_b = -1.04$ for the pK_a behavior of substituted benzylamines.[17a] These data permit an estimate of $\rho_a \sim +0.5$ to $+1.3$ for the imine-forming elimination. However, it must be cautioned that this is a very tenuous estimate since the models for obtaining ρ_b are quite dissimilar to the reaction under consideration.



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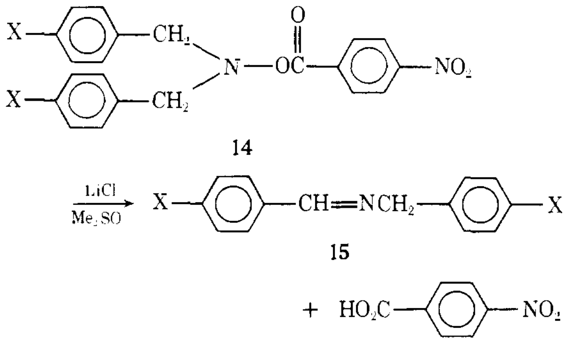
It is clear from these arguments, however, that ρ_a will probably be greater than $+0.5$ and this is in keeping with a polar elimination as the second step of the reaction. While few studies of imine-forming eliminations are available, it is known that such eliminations are quite facile relative to analogous olefin-forming eliminations.[20] Both *N,N*-dichloro amines[21a] and *N,N*-difluoro amines[21b] undergo elimination to the *N*-halo imine under quite mild conditions compared to analogous olefin-forming reactions.[22] Furthermore, the production of *N*-benzylidenebenzylamines, **15**, from *N,N*-dibenzylhydroxylamine *O*-*p*-nitrobenzoate (**14**) (eq 10) is promoted by bases such as azide and chloride in Me_2SO.[23] In this study, very little substituent effect (X = H, CH_3, Cl) on the rate of elimination was found while benzylic deuteration gives $k_H/k_D = 8.1$. These data were used to formulate an E2 type of elimination as the mechanism.



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(10)

The low ρ_a and the isotope effect $k_H/k_D = 4.2$ for imine formation in the present study are also consistent with a base-catalyzed polar elimination of **11**. These data also suggest that the transition state for this elimination is characterized by a high degree C–N π-bond formation, a high degree of proton transfer, and a high degree of N–O bond heterolysis in structure **12**. This late transition state is expected, by analogy to carbon systems,[7a] because the catalyzing base is weak and the leaving group is good. In contrast the poor leaving ability of the carboxylate group in **14** and the basic nature of Cl^- in Me_2SO solution[24] would contribute to an earlier transition state and hence the larger isotope effect $k_H/k_D = 8.1$. The small substituent effect in the latter case is somewhat puzzling although only limited data are available. It is encouraging that the present data for imine-forming eliminations tend to parallel the data obtained for olefin-forming eliminations.

The regioselectivities measured for the oxidation of *N*-alkylbenzylamines are in accord with both the polar nature of the elimination and a late transition state for the imine-forming elimination step. From the results given in Table IV it is evident that increased branching in the *N*-alkyl group leads to a greater amount of alkyl proton removal. This is presumably due to the formation of a more highly substituted imine, and is consistent with a late transition state during the imine-forming elimination. A late transition state would better reflect the greater stability of more highly substituted imines[25] and thus the regioselectivity of the oxidation would change in their favor, as is observed. On the other hand, if an early transition state were involved in the elimination step, the regioselectivity should be somewhat dependent on the acidity of the proton being removed.[26] Increased branching in the alkyl group should lower the acidity of the alkyl group proton and thus its removal should be less favorable, in opposition to the experimental results.

The measured regioselectivities also argue against the involvement of electron transfer in the oxidation of amines by sulfonyl peroxides. Rosenblatt et al.[9b,c] have studied the chlorine dioxide oxidation of *N*,*N*-dimethylbenzylamines which proceeds by an electron transfer process analogous to eq 2. A regioselectivity of benzyl to methyl cleavage of 0.74 was noted as compared to the value of 5.0 in this study. Furthermore, it has been shown for radical cation amine cleavages that the most acidic proton is preferentially lost.[27] This is again contrary to the present results so that an electron transfer mechanism is discounted.

The use of sulfonyl peroxides as general two-electron amine oxidants can be developed since multiple oxidative pathways are not supported by the present data. Furthermore, the use of conductance methods in studying the oxidation of amines with sulfonyl peroxides provides an effective method for investigating base-catalyzed, imine-forming eliminations. Heretofore unavailable information may thus be obtained.

Experimental Section

Melting points were taken on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 137 spectrometer. NMR spectra were recorded on a JEOL PS-100 NMR spectrometer, and mass spectra were recorded on a Hitachi RMU-6 instrument. Gas chromatographic analyses were performed on either a Varian Aerograph Model 920 or A90-P3 instrument. Yields were measured by addition of an appropriate standard and chromatography on one of the following columns: column A, ¼ in. × 6 ft, 5% QF-1 on Anachrome ABS 80/90; column B, ¼ in. × 7.5 ft, 5% DC 704 on Anachrome ABS 80/90; column C, ¼ in. × 8 ft, 10% Carbowax 20 M-2% KOH on Anachrome ABS 80/90. Detector response factors were calculated from known mixtures of compounds being analyzed and these were applied to the raw peak area data.

Amines. The amines used in this study were either commercially available or were prepared from the commercially available benzyl halides by the Sommelet procedure.[28] *m*-Trifluoromethylbenzylamine was prepared by the lithium aluminum hydride reduction of the nitrile,[29] benzylamine-α,α-d_2 was prepared by lithium aluminum deuteride reduction of benzonitrile by the same method, and *N*-(*n*-heptyl)benzylamine was prepared from *N*-(*n*-heptyl)benzamide[30] by lithium aluminum hydride reduction.[31] In all cases the amines were purified by conversion to the hydrochloride salt with 2.5 M HCl. The aqueous solution was extracted with ether, reduced in volume by distillation, and cooled to precipitate the ammonium salt which was filtered and dried in air. The free amine was generated with excess KOH, extracted into methylene chloride, and dried (Na_2SO_4). Methylene chloride was removed, and the amine was distilled under reduced pressure and stored in serum cap sealed bottles under a nitrogen atmosphere. It was necessary to guard against atmospheric exposure during storing, handling, and transfer so that carbamate formation by absorbed CO_2 could be minimized. If this precaution was not taken, results of both competitive and kinetic experiments were somewhat erratic.

General Procedure for Amine Oxidations with 1a. All preparative oxidations (e.g., Tables **III**, IV) were carried out similarly and a typical oxidation is described. A solution of benzylamine (0.642 g, 6.0 mmol, 4 equiv) in ethyl acetate (5 mL) under nitrogen was added in one portion by syringe to a suspension of **1a** (0.6 g, 1.5 mmol)[32] in ethyl acetate (35 mL) which was prepared under nitrogen and cooled to −78 °C. The mixture was stirred magnetically at −78 °C for 2 h and the solvent was removed on a rotary evaporator *without the application of heat.* Hydrochloric acid (2 N, 50 mL) was added to the pasty, often pale yellow residue and the mixture was placed in a bath preheated to 150 °C and distilled until 15–20 mL had been collected. Saturated sodium bicarbonate (20 mL) was added to the steam distillate after which it was extracted with ether (3 × 10 mL). The ether extracts were dried ($MgSO_4$), a suitable standard was added, and the mixture was analyzed by gas chromatography on either column A at 80 °C or column B at 100 °C. The carbonyl products were identified by collection and conversion to the known 2,4-dinitrophenylhydrazone derivatives. The yields of aldehyde products from benzylamines **4a–f** are given in Table III and the yields of benzaldehyde from *N*-alkylbenzylamines **8a–d** are given in Table IV.

Competitive Oxidation of 4a–f with 1a. Mixtures of **4a** and a substituted analogue **4b–f** were oxidized identically. A typical procedure is as follows. Benzylamine (1.61 g, 15.0 mmol) and *m*-chlorobenzylamine (2.83 g, 20.0 mmol) were added by syringe to a nitrogen-filled flask and diluted with ethyl acetate (5.0 mL). This mixture was cooled to −20 °C and added by syringe to a solution of **1a** (0.6 g, 1.5 mmol) in ethyl acetate (50 mL) which was prepared under nitrogen and cooled to −78 °C. The oxidation mixture was then stirred and worked up exactly as described above for the general oxidation procedure. The product mixture was analyzed for benzaldehyde and *m*-chlorobenzaldehyde by VPC. Standard mixtures of these aldehydes were prepared and analyzed to obtain detector response factors. The amounts of aldehydes obtained from the oxidation were corrected for the disparate amounts of starting amines and the resulting ratio is given as $k_{1\,\mathrm{rel}}$ in Table I. In this experiment, a standard (*p*-chlorobenzaldehyde) was added and the total yield of carbonyl products was 75%.

To check the method, a mixture of **4b** and **4d** was oxidized analogously and a relative ratio of 0.69 was obtained, which compares well with the value of 0.68 from the competitive oxidations of the individual amines.

Conductance Method. Conductance measurements were made with the apparatus shown in Figure 3. A stabilized 60-Hz ac variable voltage source[33] was used to supply voltage (typically 1.18 V) to the conductivity cell (Thomas, cell constant 1.0) which was connected to

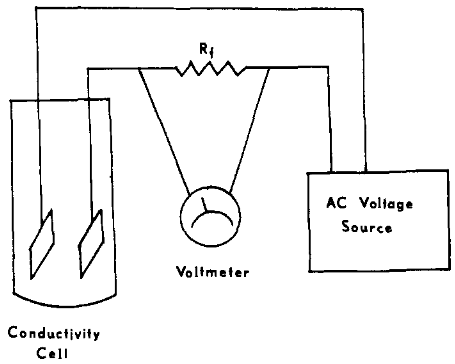

Figure 3. Apparatus for measuring conductance of amine-sulfonyl peroxide reaction.

series to a fixed resistor R_f (1000 Ω). A Hewlett-Packard 3465A digital multimeter was used to measure the voltage drop across R_f during the kinetic run and to ensure that the voltage to the entire system remained constant over the kinetic run. The cell was equilibrated at −9.7 ± 0.1 C before and during the run.

A typical kinetic run is described as follows. Benzylamine (278.3 mg) was added by syringe to a 50-mL volumetric flask which was filled with nitrogen and fitted with a syrum cap. The flask was filled to the mark with 3 M H_2O in tetrahydrofuran[34] which had been equilibrated to −9.7 °C and the amine solution placed in a constant temperature bath at −9.7 °C. Peroxide **1a** (30.3 mg) was placed in a 25-mL volumetric flask, diluted with ethyl acetate,[34] and cooled to −9.7 °C, after which it was made up to the mark with a small additional quantity of ethyl acetate. A kinetic run was initiated by placing 15.0 mL of the amine solution in the conductivity cell and adding 5.0 mL of the peroxide solution to give a reaction mixture that was 0.039 M in amine and 0.0075 M in peroxide. The voltage drop (V_f) across the fixed resistor R_f was measured at intervals. The infinity point ($V_{f\infty}$) was determined by removing the cell from the bath, warming to 30 °C for 1 h, and measuring V_f after replacing in the cooling bath. At least four amine concentrations for each amine were used and each run was duplicated with excellent agreement (<5% deviation). Plots of ln $1/(V_{f\infty} - V_f)$ vs. time were used to obtain pseudo-first-order rate constants (k_{obsd}) and plots of k_{obsd} vs. [A] were used to obtain the second-order rate constant k_2 (Table II).

In the above treatment V_f was used as a measure of conductance. This can be shown by considering the circuit. The input voltage V_0 is given by

$$V_0 = IR_c + IR_f$$

where R_c is the resistance of the cell and R_f is the fixed resistor. Since $R_c \gg R_f$, $V_0 \cong IR_c$ and $I = V_0/R_c$, the measured quantity V_f is given by $V_f = IR_f$ and by substitution $V_f = V_0R_f/R_c$. Since conductance $L = 1/R_c$ and V_0 and R_f are constant, $V_f = V_0R_fL$ or $V_f = cL$ where c is a constant. It is seen that V_f is directly proportional to the conductance. Since it was determined that the conductance is linearly related to concentration in the range of interest (vide infra), and since pseudo-first-order conditions were employed, it can easily be shown from the rate equation that ln $1/(V_{f\infty} - V_f) = k_{obsd}t - \ln(V_{f\infty} - V_{f0})$ and thus k_{obsd} is obtainable from V_f measurements. A typical plot is given in Figure 4 for *p*-chlorobenzylamine (**4d**).

The rapid conductance increase upon mixing was observed for all the amines (**4a–f**) used. Benzylammonium *p*-nitrobenzenesulfonate (**7a**) was prepared from benzylamine and *p*-nitrobenzenesulfonic acid in ether. Solutions of **7a** were prepared by dissolution of a weighted quantity in 3 M H_2O in THF (15.0 mL) which had been equilibrated at −9.7 (5.0 mL). Concentrations ranged from 4.0 × 10^{-4} to 2.0 × 10^{-3} M and after equilibration at −9.7 °C, V_f was measured. A plot of V_f vs. concentration was linear so that $V_f \propto [7]$. By measuring the initial conductance of a reaction between **4a** and **1a**, an initial concentration of **7a** was found to be 7.6 × 10^{-4} which corresponds to the liberation of 1 equiv of **7a** upon mixing.

Determination of Regioselectivity in the Oxidation of N-Alkylbenzylamines 8a–d. The *N*-alkylbenzylamines **8a–d** were oxidized and hydrolyzed as usual and the benzaldehyde produced was analyzed on column A at 75 °C. The residue from the steam distillation was taken to pH 14 with potassium hydroxide and extracted with methylene chloride (3 × 10 mL) and dried (Na_2SO_4). A weighed quantity of aniline was added as standard, the solution was analyzed for benzylamine on column C at 210 °C.

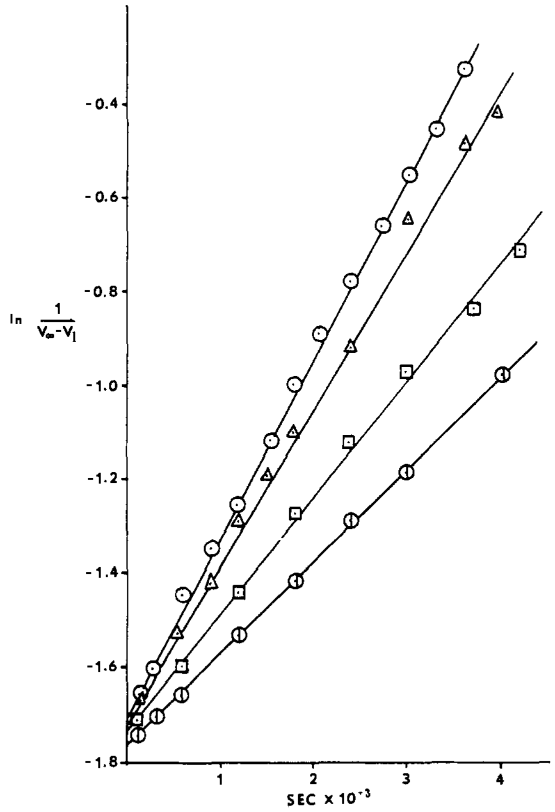

Figure 4. Plot of ln $1/V_{f\infty} - V_f$ vs. time for the oxidation of **4d** with **1a** (7.5 × 10^{-4} M). Amine concentrations are , 0.0216 M; □, 0.0272 M; △, 0.0355 M; and ○, 0.0417 M.

In the case of *N*-(*n*-heptyl)benzylamine (**8d**), both benzaldehyde and *n*-heptanal were obtained from steam distillation of the reaction mixture and analyzed on column A at 90 °C after addition of a weighed quantity of anisole as standard.

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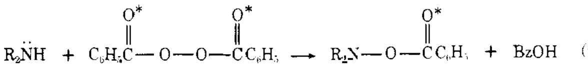

$$R_2\ddot{N}H + C_6H_5\overset{O^*}{\overset{\|}{C}}-O-O-\overset{O^*}{\overset{\|}{C}}C_6H_5 \longrightarrow R_2N-O-\overset{O^*}{\overset{\|}{C}}C_6H_5 + BzOH \qquad (i)$$

reverse reaction does not occur. In the framework of the two-step, two-electron mechanism, nucleophilic attack by the amine on the sulfonyl peroxide bond to generate **2** is considered irreversible by analogy.

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The Effect of Solvent on Intramolecular General Base Catalysis in the Hydrolysis of α,β-Unsaturated Schiff Bases

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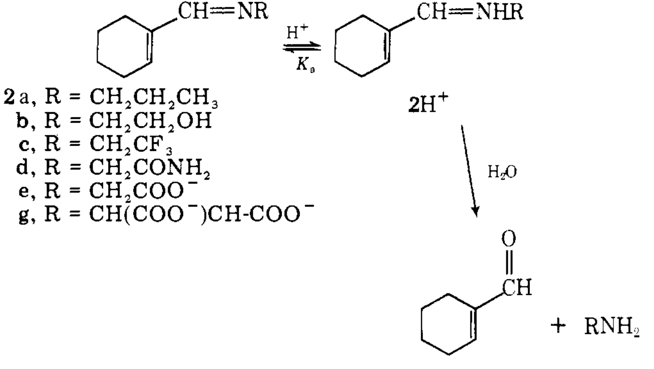
Abstract: The hydrolytic reactions of a series of Schiff bases (**2a–g**) derived from cyclohexene-1-carboxaldehyde were examined in 50% (v/v) aqueous dioxane. The rate constants for water attack on the protonated Schiff bases ($k_1^{H_2O}$) showed relatively small rate enhancements (3- to 12-fold) over the corresponding rate constants in water, while accelerations in the rate constants for the acetate-catalyzed attack of water were somewhat larger (17- to 50-fold). A linear correlation of log $k_1^{H_2O}$ with Schiff base pK_a in 50% dioxane (slope = −0.95 ± 0.08) revealed that the rates of water attack for Schiff bases derived from glycine (**2e**) and aspartic acid (**2g**) were >10^3-fold larger than predicted, owing to intramolecular general base catalysis by internal carboxylate groups. Analogous to results obtained in purely aqueous solution, carbinolamine breakdown occurs through both zwitterionic and protonated carbinolamine intermediates in aqueous dioxane. The effect of decreased solvent polarity on the various rate constants reflecting rate-limiting carbinolamine breakdown was investigated and it was found that the breakdown of the protonated carbinolamine is also enhanced by the internal base in **2e**.

Introduction

Previous work has suggested that the hydrolytic reactions of Schiff bases are accelerated in aqueous dioxane solvents relative to water, despite the fact that the concentration of water is decreased.[1] In addition to modest increases in the uncatalyzed attack of water, the general base catalyzed process shows large rate enhancements in dioxane-water mixtures. In a preceding paper[2] we investigated the hydrolysis of a series of α,β-unsaturated Schiff bases (**2**) in water with a variety of imino substituents. The efficient intramolecular general base catalysis observed for **2e** and **2g** in water prompted us to examine the possible enhancement of such catalysis in less polar solvents, analogous to the acceleration observed for the intermolecular process.



2a, R = $CH_2CH_2CH_3$
b, R = CH_2CH_2OH
c, R = CH_2CF_3
d, R = CH_2CONH_2
e, R = CH_2COO^-
g, R = $CH(COO^-)CH\text{-}COO^-$

1

Results

The hydrolysis of the α,β-unsaturated Schiff bases **2a–g** was studied in 50% aqueous dioxane at 25.0 °C (μ = 0.5 with KCl). The reaction was followed spectrophotometrically at 260 (low